Performance of Tyrer Cuzick model for Breast cancer risk assessment among Pakistan's female population

Abstract

Background: Breast cancer incidence is highest in Pakistan among Asian countries. The known risk factors include family history, hormonal exposure, benign proliferative diseases etc and are included in tyrer cuzick model with addition of mammographic density. The models need validation studies to implement in prediction and screening and prevention strategies among different populations. This study aims to validate tyrer cuzick model for Pakistan's females.

Methods and materials: 317 biopsy proven breast cancer patients from breast surgery clinic at Liaquat national hospital were included. The 10 years risk score is calculated by applying the tyrer cuzick model software. Subcategories of low risk <2%, moderate risk 2-7% and high risk >8% were identified. Further risk group stratification is done to find association with individual factors i.e., age group, menopausal status, family history and mammographic density.

Results: The mean tyrer cuzick score was low to moderate i.e. 2.23±1.66. The score was distributed as low risk 174(54.9%), moderate risk 137(43.2%) and high risk 6(1.9%). Low risk was observed among 116(81.7%) of less than 50 years old, 105(78.9%) premenopausal, 113(59.8%) with no family history and 120 patients (59.7%) with low mammographic density. Most of the moderate risk was found in 113(64.6%) of more than 50 years old, 109(60.2%) with postmenopausal, 24(61.5%) with family history, 58(50%) with high mammographic density respectively.

Conclusion: The tyrer cuzick model can predict risk for developing breast cancer among Pakistan population close to accurate among older age, postmenopausal, family history of breast cancer and high mammographic density.

Keywords: Tyrer cuzick model, validation, mammographic density.

Introduction

Breast cancer is the most commonly diagnosed and the leading cause of death among the female population. According to Globocon 2020, numbers of new cases were reported to be 2.26 million (11.7% of all sites) and the numbers of deaths 684,996(6.9%

of all sites)(1). The incidence inEast Asian population was 43.3% with a cumulative risk of 5.2% and mortality rate was 9.9% (age standardized per 100,000) as of Globocon,2020(2). In Pakistan, breast cancer is the most frequently diagnosed cancer and has the highest incidence among the Asiancountries i.e., 34,066(19.6%)(3) and highest death rate of 115% (2). The numbers in Asia, although lower than western world, are increasing overtime due to advances in diagnostic facilities but still locally advanced cases and metastatic disease are more common. These demographics highlight the importance of identifying the high risk groups and devising screening strategies and preventive measures. Although age is the criterion for starting the screening programs globally, the implementation of risk based screening is important(4). Risk evaluation models like Tyrer Cuzick can help in identifying the high risk group and targeted screening for this group can be a way to efficiently utilize the resources

Breast cancer is attributable to multiple risk factors and have been studied extensively for quantitative risk estimates. They can be broadly divided into four groups: family history (genetic), hormonal, proliferative benign breast disease such asatypical ductal hyperplasia and dense mammographic density and high mammographic density(5). A variety of risk estimation models combining different sets of factors have been developed and researched for accuracy and validation in different populations. These models include Breast Cancer Risk Assessment Tool ‘BCRAT’ model, Breast Cancer Surveillance Consortium ‘BCSC’ model, International Breast Cancer Intervention Study ‘IBIS’ (Tyrer Cuzick) model(6), BRCAPRO model and Gail, Claus, Ford models. The models have to be validated for the target population before using them for identification of high risk groups for screening and prevention purposes(7).

Improvements in survival and outcome of breast cancer patients can be achieved with early detection through screening(8). The Tyrer Cuzick model has not been validated for application in the Pakistani population. So through this study we aim to assess the performance of this model and applicability on the female population in Pakistan.

Materials and methods

Study population: The prospective cross-sectional study is performed at Breast surgery clinic, General Surgery Department of Liaquat National Hospital, Karachi. All female patients included in the study were diagnosed with breast carcinoma by histopathology. Appropriate sample size was calculated using the WHO software and a sample of 317 patients were selected in the study from January 2020 to April 2021. Male patients were excluded from the study. Informed consent of the included patients taken before starting the data collection.

Data collection procedure: A questionnaire was formulated based on the risk factors included in the Tyrer Cuzick model I.e., age, weight and height, age at menarche, parity

status, age at first birth, menopause state, previous biopsy and histopathology, hormonal therapy use, duration of hormonal therapy use, mammographic density, family history including breast or ovarian cancer, degree of relative and age at diagnosis. The questionnaire for each patient was filled from the data in history performa of the breast clinic file records taken by the residents. The data was entered in the IBIS model software package available online (http://www.ems-trials.org/riskevaluator/) to calculate the 10 year risk score for individual patients.

Data analysis procedure: Data was entered and analyzed using Statistical Package for the Social Sciences (SPSS-version25). Mean and standard deviation were calculated for age, age at menarche, menopause, first pregnancy, height, weight. Frequencies and percentages were computed for BMI, menopause status, mammographic density, prior biopsy and family history. Chi-square/Fisher-exact test was applied for association among the qualitative variables i.e., age, menopause status, mammographic density and family history. P-value ≤0.05 was considered as statistically significant. According to the 10 year risk score the data is distributed into 3 groups: low risk <2%, moderate risk 2-7% and high risk >8%. The risk is than stratified for the age group (<50 years and >50 years), menopause status (pre- and post-), family history of breast cancer(positive or negative) and mammographic density(low, ACR type A and B and high, ACR type C and D) individually.

Results

Sample characteristics: Total 317 patients diagnosed with breast cancer were included in our study. The mean age of the patients were reported as 50.76±12.47 years. 175 (55.2%) of them were more than 50 years old. Mean age at menarche was 13.12±2.58. The mean height and weight was found as 155.76±11,06m and 70.97±15.98 kg. Their parity was noted as 48(15.1%) nulliparous, 267(84.2%) parous and 2(0.9%) unknown. We found 7(2.2%) had prior biopsy and 2(0.6%) had LCIS. Their menopausal status was found as 134(42.0%) premenopausal and 181(57.2%) postmenopausal. Only 1(0.3%) had hormonal therapy. Their mammogram density was contributed as 26(8.2%) had type A, 175(55.2%) had type B, 114(36.6%) had type C and 2(0.6%) had type D. 39(12.3%) had a positive family history. The detailed descriptive statistics is presented in Table.01

Performance assessment of the tyrer cuzick model: The mean tyrer cuzick score was 2.23±1.66. The risk according to the scoring was distributed as 174(54.9%) had low risk, 137(43.2%) had moderate risk and 6(1.9%) had high risk. (Table.02)

Association with individual risk factors

The young age group were mostly in the low risk 116(81.7%) compared to the old age group 58(33.1%). Those above 50 years old fell into the moderate and high risk groups 113(64.6%) and 4(2.3%) respectively higher than the younger age population 24(16.9%) and 2(1.4%). (P<0.0001)

The highest number of postmenopausal women lie in the moderate risk group 109(60.2) and the premenopausal lie in the low risk group 105(78.9%). The percentage of premenopausal women in the moderate group were 25(18.8%) and the high risk group were 3(2.3). 38.1% of postmenopausal women had low risk and 1.7% in high risk group. 17.1% women had a positive family history and among them 61.5% are in the moderate and 7.7% are high risk while low risk is 30.8%. 59.8% of patients with negative family history predicted to have low risk, 39.2% moderate risk and 1.1% high risk. (P value 0.0001)

Patients with high mammographic density (ACR type A and B) were predicted to have moderate risk 58(50%) and high risk 4(3.4%) while 120(59.7%) patients with low mammographic density were given low risk by the tyrer cuzick model. (P value 0.05)

The mean tyrer cuzick model score for our sample population is 2.33±1.66. 1.9% and 43.2% of the population predicted to have high and moderate scores. As all our patients are diagnosed with carcinoma breast, the results show that the tyrer cuzick model is more predictive of the risk in old age groups (>50 years), postmenopausal, family history for breast cancer and high mammographic density type (type C and D). It underestimated the risk in the old patients (>50 years), premenopausal, with no family history and low mammographic density. The detailed association of factors with tyrer cuzick levels is presented in Table.03

Discussion

Tyrer Cuzick model is the most extensive among others because it includes all four groups of the risk factor. The addition of previously infrequent studied risk factors i.e. mammographic density adds significant predictive value to this model for risk stratification(8, 9). Many comparative studies have been done to find the most accurate risk evaluation model. The Tyrer Cuzick model was found to have the most accurate risk estimation of high risk groups based on family history and hormonal factors while Gail, Ford and Claus underestimated the risk in these groups and needed improvements(10). In this study, the four models were applied to 1933 women attending the screening clinic and accuracy was evaluated using the ROC curve. The area under the curve was 0.735 for Gail, 0.716 for Claus, 0.737 for Ford, and 0.762 for Tyrer–Cuzick making it the most accurate model among others(10). In another study, IBIS or Tyrer Cuzick and BCRAT or Gail model were evaluated for performance considering the genetic and non-genetic risk factors included in these models(11). The risk calculated by the Gail model was significantly lower than the observed risk while IBIS calculated risk was generally near to the observed risk. The Gail model was applied for female breast cancer patients of tertiary care hospitals in Pakistan and over-estimated the risk for the older age groupsuggesting the need of evaluation of other models for our population(12).

McCarthy and colleagues studied the model performance of BRCAPRO, IBIS And BOADICEA (Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm) on 35,921 predominantly white women who came to the Newton-Wellesley Hospital in Massachusetts for mammographic screens between 2007 and 2009. The importance of further studies before adapting these models for other countries with different races and ethnicity around the world was highlighted(13). In one study, the Tyrer Cuzick model was applied for Asian and white British/Irish women in the UK and Asian women coming for screening were found to have lower risk of developing breast cancer. Age-standardised incidence was 3.2 (95%CI 1.6-5.2, 18 cancers) per thousand women/year for Asian women vs 4.5 (95%CI 4.2-4.8, 1076 cancers) for white British/Irish women(14). The characteristic of Asian population were different than the western population i.e., Asian female were shorter, less obese and less likely to drink alcohol and preventive measure could intent to reduce modifiable risk factors.
In another study, 91,893 women were recruited from 1993-1998 and follow-up done for a median period of 18.9 years, 6836 new breast cancer cases were diagnosed. The model was well-calibrated (O/E 0.95) in NHW and African Americans, but it over-estimated risk for Hispanics (O/E 0.75). Results suggested good calibration for Asian/Pacific Islanders and Native Americans, but sample sizes were small(15)
In our study the breast cancer patients were predicted to have a score of 2.33±1.66. If we subcategories the score, 54.9% of the patients were in the low risk group, 43.2% of the breast cancer patients fall in the moderate risk group and only 1.9% in the high risk. These results show under prediction of risk among breast cancer patients. This highlights the need of risk model comparative studies and risk factor stratification for the Pakistani population and development of a model that can predict the risk more accurately.
If the score is analysed for individual risk factors it is seen that it predicted risk comparable to observed risk for patients with old age, postmenopausal, family history of breast cancer and high mammographic density. The risk was observed to be lower for the young age group, premenopausal women, no family history of breast cancer and low mammographic density. We can say that the risk factors for breast cancer differ in our population compared to the western population e.g. most women are multiparous, have first birth at young age etc. and hence there is a need to identify the risk factors and devise different risk calculator tools and meanwhile to assess the different risk model for Pakistan's female population in prospective studies.

Conclusion

In summary we found that Tyrer cuzick model is predictive of risk among the patients with known breast cancer risk factors I.e., age more than 50 years, postmenopausal, having family history of breast cancer and high mammographic density. While in the

group with age less than 50 years, premenopausal, low mammographic density and negative family history, it underestimated the risk of breast cancer. Hence, the Tyrer cuzick model can be used for assessment of the population with the risk factors (i.e., postmenopausal, positive family history and high mammographic density etc.). However, Investigating for new risk factors in Asian population and addition into the model might help in identifying the high risk population.

Disclaimer:

Tables and figures

Table-01: Characteristics of the sample population

Variable	**Study population** (n=317)
Age (years)	50.76±12.47
<50	44.8%
>50	55.2%
Height	155.76±11.02
Weight	70.97±15.98
Age at menarche	13.12±2.58
Age at first pregnancy	23.39±4.98
Age at menopause	47.49±6.09
BMI	30.34±17.12
Obese	38.8%
Non obese	61.2%
Parity	
Nulliparous	15.1%
Parous	84.2%
Prior biopsy	

Yes	1.90%
LCIS	0.6%
Menopause status	
Pre menopause	42.3%
Post menopause	57.1%
Hormonal therapy	0.3%
Mammographic density	
Type A	8.2%
Type B	55.2%
Type C	36%
Type D	0.6%
Family history	17.1%

Table-02: Tyrer Cuzick score

Mean Tyrer Cuzick score	2.23±1.66
Tyrer cuzick score	
Low Risk(<2 score)	54.9%
Moderate Risk(2-7 score)	43.2%
High Risk(>8 score)	1.9%

Table-03: Association of age group, menopause status, family history and mammogram status with Tyrer cuzick levels.

	Tyrer cuzick score	

Risk factor	<2	2-7	>8	P Value
Age				
<50 years	116(81.7%)	24(6.9%)	2(1.4%)	<0.001
>50years	58(33.1%)	113(64.6%)	4(2.3%)	
Menopause status				
Premenopausal	105(78.9%)	25(18.8%)	3(2.3%)	<0.001
Postmenopausal	69(38.1%)	109(60.2%)	3(1.7%)	
Family history				
Positive	12(30.8%)	24(61.5%)	3(7.7%)	0.001
Negative	113(59.8%)	74(39.2%)	2(1.1%)	
Mammographic density				
Low (A&B)	120(59.7%)	79(39.9%)	2(1.1%)	0.03
High (C&D)	54(46.6%)	58(50%)	4(3.4%)	

Chi-square/Fisher Exact test is applied.

Significant at p-value ≤0.05

Insignificant at p-value >0.05

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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